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Title of Project: Metabolic Changes in Humans Following Total Body Irradiation

Report Period: November 1, 1961 - April 30, 1963

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I. INTRODUCTION:

This report summarizes the work and interpretation of studies carried out on 19 patients given whole body irradiation. Ten additional patients received similar exposures and one received nitrogen mustard but because of the progression of far advanced disease and other factors they are excluded from this report. Some material from the Summary Report of November 1961 will be included so as to indicate the continuity of the investigations. The project was begun in February 1960 and this report includes data through April 30, 1963.

2. AIMS AND SCOPE OF THE PROJECT:

These studies are designed to obtain new information about the metabolic effects of total body and partial body irradiation so as to obtain a better understanding of these acute and subacute effects in human beings. This information is necessary to provide knowledge of combat effectiveness of troops and to develop additional methods of diagnosis, prognosis, prophylaxis and treatment of these injuries.

The parameters which have been investigated during the past three years are listed in Table I.

TABLE I

Parameters Studied for Whole Body Radiation

A. Continuing

1) Clinical findings
2) Hemogram and profile scores
3) Miscellaneous laboratory tests (electrolytes, renal function, etc.)

B. Terminated

1) Aminoaciduria
2) Creatinuria
3) Serum electrophoresis and immunoelectrophoresis
4) Antibody changes after administration of bacteriophages (May be reactivated)

C. Under Active Investigation

1) Deoxycytidine and other nucleotides in urine
2) Xanthurenic acid in urine
3) Chromosome changes in white cells
4) Quantitative precipitin test (Dr. Luzzio, Army Medical Research Laboratory, Ft. Knox, Ky)
5) Levels of serum lipoproteins (Lt. Col. E.C. Knoblock, Walter Reed Army Institute of Research)
6) Preliminary design of psychological and physiological tests of fitness or performance
7) Use of autologous marrow

The parameters which have been terminated are those in which no clearly defined radiation changes could be demonstrated.

During the period of this report (November 1961 - April 1963) patients were studied at dose levels of 150 - 200 rad. These doses are equivalent to midline air doses of 226 - 336r.

3. SELECTION OF SUBJECTS:

This problem has been somewhat more difficult than originally anticipated. Only individuals with metastatic or incurable neoplasms are eligible for such studies. At first patients who had received previous partial body radiation and/or chemotherapy were included. The clinical and laboratory findings in these patients indicated that the response to total body radiation was confounded by the previous treatment as well as by the underlying disease. This problem has been ameliorated by selection of patients who usually have not had previous radiation and have not had chemotherapy. The problem of the underlying disease remains. They must be in relatively good nutritional status and with a stable hemogram. Renal function must be normal. Patients with lymphomas are excluded although occasionally such patients have been treated in the past. Bronchogenic carcinoma is no longer accepted. Patients with solid neoplasms which are not radiosensitive are sought.

4. TECHNIQUE OF STUDY:

The design of the study is such that the patient serves as his own control. A pre-irradiation control period of 10 days to 2 weeks has continued to be utilized. However, with the increased dose of radiation, the post-irradiation period has been extended to 6 or 8 weeks.

Five observations are made in the pre-irradiation period. Observations currently made are listed in Table II. Post irradiation specimens are then obtained at standard test times as described by Thoma and Wald (See section on Analysis of Data).

Patients have been studied on the Tumor Ward and Psychosomatic Ward of the hospital. However a Metabolic Ward has now been opened and patients to be studied will be placed on it. One bed has been allotted for this study.

During the pre-irradiation period, the patient's records are reviewed by the physicians to be certain that the contribution of the underlying disease can be evaluated. One or two sham irradiations are given to permit accurate dosimetry and obtain cooperation by the patient. The patient is told that he is to receive treatment to help his disease. There is no discussion of possible subjective reactions resulting from the treatment. Other physicians, nurses, technicians and ward personnel are instructed not to discuss symptoms or reactions with the patient.

5. ANALYSIS OF DATA:

Collection of data continues essentially according to the plan of Thoma and Wald (J. Occup. Med. 1:420-447, 1959) and described in section 3 of Medical Aspects of Radiation Accidents, E.L. Saenger, ed., U.S. Government Printing Office, 1963.

All data are recorded on score sheets and then transferred to IBM cards. Thus all information together with the appropriate machine programs is available for analysis by other centers or interested individuals.

6. DOSIMETRY:

a) Cobalt-60

The radiation is delivered by a Cobalt 60 Teletherapy Unit under the following exposure conditions.

The radiation beam is directed horizontally at a wall 338 cm. away

with the patient midline at 282 cm. from the source. The beam area for the 50 percent isodose curve at the patient midline distance is a square approximately 67 cm. by 67 cm. The patient is placed in a sitting position with legs raised and head tilted slightly forward. The irradiation is given by delivering half the specified exposure laterally through one side of the patient. The patient is then turned over and the other half exposure delivered laterally through the other side.

The variation of air dose with distance from the source was determined with a Victoreen 25r chamber. The results indicated no departure from the inverse square law relationship for distances used in the study. Therefore, no correction was required for a possible dose contribution to the patient due to backscatter from the wall.

Preliminary measurements were made in a masonite phantom using dosimeters placed on lateral surfaces and at the midline of the head, trunk and knee portions of the phantom. These results are shown in Figure I. It is seen that if the midline doses to the trunk, head, and knees are compared, the maximum variation in these doses is about 16 percent.

The exposure to the patient was determined as follows. The percentage depth dose at different depths for a 400 cm^2 field area and a source-skin distance of 80 cm is given by Johns (1). The depth dose at the greater source-skin distances used for the patients was found by multiplying the depth doses at 80 cm by the "F" factor postulated by Mayneord and Lamerton (2).

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(1) Johns, H.E., "X-rays and Teleisotope Gamma-rays," Radiation Dosimetry. Edited by G.J. Hine and E.L. Brownell. Academic Press Inc., New York, p.562.

(2) Mayneord, W.V. and L.F. Lamerton. Brit. J. Radiol. 14:255, 1941.

$$F = \frac{(D_d)^{f_2}}{(D_d)^{f_1}} = \left(\frac{f_2}{f_1}\right) \times \left(\frac{f_1 + d}{f_2 + d}\right)$$

where f_1 and f_2 are source-skin distances and d is the depth.

By using the corrected depth dose at the patient midline (one-half lateral dimension of the trunk) and a conversion factor of 0.97 rads per roentgen for Cobalt gamma radiation, the surface dose and midline air dose required to give a desired midline absorbed dose in rads was calculated.

A direct comparison of the calculated and measured (phantom) doses was made for one patient who had the same lateral trunk dimensions as the phantom. The relative depth dose for each lateral exposure to this patient is given in Figure 2. The doses indicated by crosses are measurements made in the phantom and compare quite well with the calculated doses. The combined dose of the two radiation fields is also given in this figure and shows a good homogeneous dose distribution through this patient. The maximum variation in lateral dose distribution was $\pm$ 13 percent for one patient having a lateral trunk dimension of 36 cm.

The dosimetry for the nineteen patients of interest is given in Table III. The patients treated from February 1960 through October 1961 received midline air doses of 85 - 185r; those treated subsequently received midline air doses of 155 - 336r. Treatment time was 1/2 - 1 hour. Dose rates were 3 r/min to 6 r/min.

7. CLINICAL OBSERVATIONS:

Ten additional patients have been studied since the last report. These patients received from 155 to 336r of total body radiation (total midline dose in air without a phantom). Clinical summaries are attached to this report as Appendix A.

We have compared the effect of previous therapy on prodromal symptomatology (Table IV). Acute symptoms of anorexia, lassitude, weakness, nausea, and vomiting are commoner in patients who have had previous partial body irradiation. These two groups did not differ in regard to their signs and symptoms during the latent period or stage of manifest illness. Nevertheless this observation suggests that individuals with previous exposure to radiation will be less tolerant of subsequent exposures. Hence troops previously exposed to 150 - 300r of whole body radiation will tend to show more combat ineffectiveness in the prodromal period than will those who are unexposed.

Patient 024 receiving 322r was the only one who had severe nausea and vomiting during administration of the radiation dose. This patient had previously received partial-body irradiation and had renal disease.

It is interesting to compare this immediate reaction and those observed by Tubiana et. al.* to our several other patients receiving total body radiation at the 150 - 200 rad level. It is likely that the nausea and vomiting observed in the patients with renal disease is due in some degree to the combination of kidney disease and radiation. Until patient 024 was treated we had been surprised by the lack of immediate nausea and vomiting which has been a striking observation

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* Tubiana et. al. (Diagnosis and Treatment of Acute Radiation. WHO, 1961, p. 235 ff).

of Tubiana et. al. in giving pre-operative therapy to individuals prior to renal transportation. His patients have well defined nausea and vomiting at about 150r so that treatment usually must be interrupted for 15 - 30 minutes.

One other patient noted nausea during irradiation.

The latent period is of 18 - 21 days as would be expected in Group I and II patients and is asymptomatic. The stage of manifest illness has been associated with bleeding and infection in several patients causing total incapacitation. In one patient (025) with a colloid carcinoma of the left lung and widespread metastases, there were anorexia, malaise, lassitude and weight loss. Leukopenia, thrombocytopenia and anemia were progressive and he died on the 34th day. A similar course was shown in another patient (021) given 200 rad died 37 days post radiation with leukopenia, thrombocytopenia and anemia. Another patient (018) receiving 200 rad died ten months after treatment. All of the patients who died showed far advanced malignancy.

Lassitude and anorexia persist in some subjects for 3 - 4 months.

Equally interesting is the observation that three of eight patients treated over 1 year ago with doses of 150 - 200 rad survive with little or no progression of their neoplasms.

8. HEMATOLOGY AND PROFILE SCORING:

Although patients with grossly abnormal hemograms are excluded from the study the patients selected cannot be considered as "truly" normal. It was found possible to correct the contribution of the underlying cancer to the hemogram by determining the profile score of Thoma and Wald (J. Occup. Med. 1:420-447, 1959) prior to irradiation and using this score as a constant correction in the post irradiation period. We assumed that within 4 - 8 weeks after

exposure the daily contribution of the underlying disease would be constant. Using this correction, the hematological results appeared to correlate well with dose and clinical course and it appears to be a useful method of partionin. radiation effect and underlying disease.

Lymphocytopenia immediately after treatment has not been found in contrast to other studies. No abnormally large polymorphonuclear leukocytes or bilobed lymphocytes have been detected.

Profile scoring was continued in the manner described in Appendix B. Delineation of disease score, radiation score and total continued to be of value in ascribing the importance of radiation in precipitating demise. "Net erythrocyte" score was again used. In this group of patients "net erythrocyte" score did not introduce significant change from a score based on the hematocrit. Table V summarizes the data based on profile scoring.

9. TERMINATED STUDIES:

a) Aminoaciduria

In normal human beings receiving external gamma and neutron irradiation from radiation accidents, aminoaciduria particularly of β aminois - butyric acid and taurine has been described (Rubin et. al. Proc. Soc. Exp. Biol. & Med. 100:130, 1959 and Gerber et. al. Rad. Res. 15:314, 1961). The excretion levels have exceeded values found in other normal population samples but of course there was no opportunity to obtain pre-treatment control levels in these accident victims. Our cancer patients had a two week control period

and two episodes of sham irradiation. Quantitative two dimensional chromatography of all urines were performed in most patients prior to 1963. Twenty acids were analyzed. There were no statistical differences in pre and post irradiation levels of individual or pooled urinary aminoacids. Several patients showed high spikes of certain aminoacids either just before or after sham irradiation. In our clinic previous studies of children following surgery or infection showed increased aminoaciduria. Thus one is forced to conclude that elevation of aminoacids in the urine is non specific and not solely characteristic of irradiation. It may be produced by different types of stresses including psychic stress. It is possible that the psychic stress was proportional to the radiation dose in the Oak Ridge patients. Possibly the neutron fraction of the radiation exposure in the accident victims was a factor by producing an increased RBE.

b) Creatinuria:

We were unable to demonstrate creatinuria. Subsequent reports of Gerber et. al. (Rad. Res. 15:307ff, 1961) have shown creatinuria both with whole and partial body irradiation. The method is not suitable for routine use in the laboratory.

c) Serum Electrophoresis and Immunoelectrophoresis:

Serum protein fractionation was performed by paper electrophoresis. No changes after total body irradiation have been found. Therefore we have deleted this procedure.

Immunoelectrophoresis using a quantitative technique of West et al (J. Lab. & Clin. Med. 58:137, 1961) was used to study possible changes of beta 2A

and beta 2M globulins which appear to be related to the immune system. No changes were found and hence this technique has been abandoned. It does not now seem likely that changes will be found in constituents of plasma related to the immune mechanism (Hasek and Lengerova in Mechanism in Radiobiology, Vol. II, 207-229, 1960, Academic Press and Unesco Report on Effects of Atomic Radiation 164, 1962). Our findings are in accord with their conclusions.

d) Antibody Changes after Administration of Phage:

Changes in the immune system in humans in doses under 200 rad have been elusive. After discussion with Dr. Robert Good of the University of Minnesota and Dr. Clark West it was decided to study the response of individuals to two different phages before and after irradiation. The occurrence of an anamnestic response precludes the use of the same phage. It will first be necessary to demonstrate some type of constant relationship between the antibody responses in untreated patients. At present the following coliform phages are being prepared: T-2, T-4 and Phi-X 174.

These studies will be similar to many done in animals. These phages have no injurious effects in humans and are used because the antibody response is large for small doses of phage.

Because of technical difficulties in preparation of the phages this portion of the studies is at present inactive.

10. DEOXYCYTIDINE:

Because urinary aminoacids did not show specific and significant elevations following whole body radiation, a search was undertaken for breakdown products of DNA. Parizek et. al. (Nature 182:721-2, 1958) reported elevation of urinary deoxycytidine following irradiation in rats. This compound once formed is

apparently not further metabolized and is excreted. The level of excretion was directly related to radiation dose. This work was confirmed by others (Zhulanov and Romantzev, Med. Radiol (Moscow) 5:31-38, 1960 and was blocked by l-cysteine and β mercaptoethylamine. No increase was found after radiation therapy in humans (Kosyakov et al, Med. Radiol. 7:31-35, 1962). It was thought to be produced following destruction of DNA.

The methods of analysis used by these workers were chromatographic and also employed the Dische reaction. These methods also measure deoxyribose and require high levels. They are nonspecific in the presence of other urinary constituents, pigments and medications.

Therefore a sensitive and relatively specific method of analysis was needed. Procedures were developed for preparation of a purine-pyramidine fraction from urine and the separation, identification and quantitative assay of deoxycytidine (DOC). These procedures were developed using irradiated rats and subsequently applied to humans. The method is sensitive for 5 μg of DOC. The technique will be described in a separate report. The rats were given 760 rad ($LD_{50/30}$) with 250 KVP cp radiation and showed elevations of urinary thymidine and DOC within the first 3 days (See Table VI).

Subsequently two human subjects were studied. Both patients showed significant increases in urinary DOC after radiation (See Table VII) as compared to pre-exposure levels. Urine from several other patients (one after thermal burn, one after surgery and one with infection) were so analyzed but did not show significant elevations of DOC.

The significance of these observations is not yet fully evaluated. Much work is required. Further animal studies will be carried out to determine at what radiation levels DOC is excreted and whether the amounts formed are proportional to dose. In the human studies it is necessary to determine the consistency of these observations. Patients with various diseases and procedures must be studied in order to determine whether the excretion of DOC is in fact specific for radiation.

Although it seems likely that DOC is produced by the breakdown of DNA, this relationship is not yet confirmed. Studies with labeled precursors are required. Administration of H-3 labeled DOC in humans as a recovery experiment is needed. Assays of normal human urines are needed to determine the excretion of DOC in the absence both of radiation and cancer. Also studies of the presence of other nucleosides and nucleotides in blood and urine are continuing. The tissues yielding DOC must be identified.

This field of investigation has obvious important implications. Breakdown of DNA has long been implicated as the fundamental biochemical change of radiation and there is an impressive literature bearing on this point. The verification of such changes in humans in the presence of complex and vigorous homeostatic mechanisms would yield significant advances in our understanding of basic and specific alterations in metabolic pathways following radiation. The observation cited above of decrease of DOC after the administration of protective agents indicates the possibility of the use of specific prophylactic agents for the protection of humans in nuclear warfare. It is therefore our intent to expand

these avenues of research as rapidly as possible.

11. XANTHURENIC ACID:

Excretion of xanthurenic acid (XA) and other metabolites of tryptophane have been reported (Langendorff, A., in Ionizing Radiations and Immune Processes, ed. C.A. Leone, Gordon and Breach pub., New York 1962, p. 294ff). XA also occurs in the urine of patients with malabsorption syndrome, certain anemias and during pregnancy. It is not produced in the presence of the co-ferment, pyridoxal-5-phosphate which is an extremely radiosensitive compound being 100 times as radiosensitive as riboflavin.

Increased excretion of tryptophane metabolites was reported as a characteristic feature of "Hartnup" disease associated with pellagra-like skin lesions, photosensitivity, ataxia, mental aberration, and gross aminoaciduria. Further studies on a family affected with the disorder showed that while the major symptoms were not altered, the tryptophane abnormality was dependent on intestinal flora. Following sterilization of the G.I. tract with broad spectrum antibiotics, no abnormal metabolites of tryptophane were demonstrated.

Increased excretion of xanthurenic acid and kynurenin following ingestion of tryptophane has been reported in vitamin B-6 deficiency and vitamin B-6 dependency diseases. It has also been reported following tryptophane tolerance tests in patients with under-nutrition or inanition, severe liver disease, certain febrile illnesses, diseases of the intestinal tract, bronchial asthma, certain types of anemia, inoperable stomach cancer, and chronic constipation. In these instances, the abnormality can no longer be demonstrated following treatment with vitamin B-6. There is no report of tryptophane tolerance tests which were carried out following use of broad-spectrum antibiotics.

Increased excretion of tryptophane metabolites, 5-hydroxyindole acetic acid, xanthurenic acid, and kynurenin (or kynurenic acid) have been reported in animals following irradiation. Excretion of p-hydroxyphenylacetic acid has been shown to be decreased following treatment with broad-spectrum antibiotics. Urinary excretion in children increases during constipation, as well as during severe gastro-intestinal disturbance.

It was necessary to develop a new method for the assay of xanthurenic acid by concentrating the urine and separating xanthurenic acid. This method will be reported separately.

We found evidence for increase in excretion of xanthurenic acid by four of eight patients treated with 100 - 200 rad whole body irradiation (See Table VIII). Some of these patients excreted increased amounts of para-hydroxyphenylacetic acid, a tyrosine derivative, following irradiation. We also noted increased excretion of para-hydroxyphenylacetic acid by several patients following total body irradiation of 100 rad.

The excretion of XA following radiation does not appear to be a striking phenomenon as DOC excretion. The metabolism of XA is intimately related to the intestinal tract. Further studies in this area may elucidate nutritional factors to degrees of radiation injury particularly for healthy individuals as many of the changes following high doses of radiation are due to the destruction of intestinal mucosa and subsequent bacterial invasion.

12. CHROMOSOME STUDIES:

Because chromosome abnormalities have been described after many types of irradiation and since the deoxycytidine findings demonstrate a possible abnormality of human DNA metabolism it was decided to carry out serial observations for possible abnormalities.

The peripheral blood is cultured using the phytohemagglutinin technique. Only four patients have been studied to date and the analyses at present are incomplete. The patients (025, 026, 027 and 029) showed no changes in the modal number of 46 chromosomes either before or after exposure.

Following irradiation various chromosomal abnormalities were shown such as dicentric forms, breaks in arms and inversion loops. One patient (029) showed a number of polyploid cells and several cells showing endoreduplication (92 chromosomes) prior to irradiation. There was a marked increase in the number of cells showing endoreduplication following irradiation.

The analyses of slides is as yet incomplete so that accurate analysis of these data is not intended. There is evidence of chromosomal abnormalities following irradiation and this phase will be actively pursued.

13. PROPOSALS FOR HUMAN STUDY PROGRAM:

On November, 1962 Eugene L. Saenger, M.D. and Ben I. Friedman, M.D. at the request of DASA submitted An Appraisal of Human Studies in Radiobiological Aspects of Weapons Effects. In this report we indicated the need for further studies in terms of:

1. Clinical evaluation
2. Metabolic effects
3. Behavioral effects
4. Dose rate response

5. Partial body irradiation

6. Prognosis - including recovery functions

7. Therapeutic methods

It is our opinion that human radiation studies need to be expanded.

We propose to continue observing the clinical and hematolo,' c effects of gradually increasing doses of total and partial body irradiation with a Co-60 unit at the rate of 5.4r/min at 282 cm. The exposures are to be unilateral, bilateral, partial, as acute and fractionated doses. In addition we propose to establish facilities for withdrawal, storage, and reinfusion of autologous marrow. As indicated elsewhere in this report we have encountered significant hematological difficulties with a dose range of 200 - 325r. Therefore, to proceed with higher doses, we feel the need to protect our patients even if we might sacrifice their value for hematological evaluation after 2-3 weeks since the hematological effects are well documented. Once this technique has been developed as a support procedure we then anticipate increasing doses to higher levels.

Observations of the urinary excretion of deoxycytidine and xanthurenic acid, chromosomal alterations and immunologic studies will be continued. These methods do show some promise as indicators of radiation damage.

Preliminary review of physiological techniques of performance testing has begun. The use of the treadmill is being investigated as well as certain psychological tests of vision and perception. We are not certain as to whether these methods will be sufficiently sensitive for the situation to be investigated but these methods will be evaluated further and a separate note submitted.

Drs. Friedman and Max Boone visited Dr. Sidney Robinson at Indiana University and Dr. Saenger visited Dr. Ross McFarland at the Harvard School of Public Health to discuss these problems.

14. SPECULATIONS ON HUMAN EFFECTIVENESS FOLLOWING WHOLE BODY IRRADIATION

From the data presently at hand including animal work and human work (Japanese, criticality accidents and our studies) certain speculation might be pursued. In a previously unexposed human doses of 200r or less will result in little combat ineffectiveness. Above this dose, the chances of encountering difficulties increases rapidly. Marked hematologic changes occur generally between the 25th and 35th day following exposure. Maximum recovery to be obtained generally requires about 100 days.

Prodromal acute effects such as nausea, vomiting, anorexia and lassitude are of the duration of hours. Intermediate effects such as hematologic complications are to be conceived of in weeks.

A previous dose of radiation does influence the incidence of acute effects. Therefore the incidence of "combat ineffectiveness" will be significantly increased on re-exposure of an individual.

Human beings recover slowly and are quite sensitive to radiation with multi-system envolvement.

15. SUMMARY:

1. This report describes certain observations made on human beings with cancer following midline air doses of 155-336r (100-200 rad).

2. A new biochemical technique has been developed for identification of deoxycytidine, a nucleoside, found in the urine. This substance was identified in the urine of rats and of two humans following whole body irradiation but not before exposure. It was not found in human beings with thermal burns, infection or after surgery. It presumably is a breakdown product of DNA.

3. Xanthurenic acid, an end product of tryptophane metabolism has been found in the urine of four of eight patients after whole body radiation. Its production is perhaps related to pyridoxal-5-phosphate deficiency or other factors as yet unidentified.

4. Chromosomal abnormalities have been identified in white cells immediately after irradiation.

5. Human beings can tolerate doses of 200 rad (300r) relatively well as far as combat effectiveness is concerned. Blood element depression is maximal at 25 - 35 days and apparent recovery is of the order of 100 days.

It is highly likely that a second dose of radiation of the order of 200 rad will be poorly tolerated even after apparent complete recovery and will result in a significant number of individuals becoming combat ineffective immediately and being incapable of sustained or heavy work for weeks or months.

TABLE II

PRE AND POST IRRADIATION OBSERVATIONS

1. Complete history and physical examination
2. Temperature, pulse, and respiration
3. Body weight
4. Medications - Fluids, antibiotics, steroids, narcotics
5. Hematology - Hgb., RBC, W BC, Differential, Hematocrit, Platelets
   Reticulocytes, Erythrocyte sedimentation rate
6. Urine
   a) Volume
   b) Routine urinalysis
   c) Chromatography for aminoacids (frozen specimens retained)
   d) Chromatography for deoxycytidine
   e) Chromatography for xanthurenic acid
7. Serum Urea Nitrogen and Creatinine
8. Lipoproteins
9. Quantitative precipitin test
10. Chromosome studies

TABLE III

TOTAL BODY RADIATION DOSIMETRY

(19 Patients)

Month and Year of Treatment	Patient No.	Surface Dose Roentgens	Midline Tissue Dose rads	Midline Air Dose Roentgens
	004	109	66	100
	006	113	54	100
February,	007	187	100	167
1960 to	008	211	100	185
October,	010	174	100	157
1961	011	191	100	170
	013**	95	50	85
	015	185	100	166
	017	163	100	149
	018	362	200	325
	020	318	200	294
November,	021	359	200	322
1961 to	022	277	150	248
April, 1963	023	374	200	336
	024	359	200	322
	025	261	150	226
	026	179	100	155
	027	279	150	238
	029	303	150	257
Range		95-374	50-200	85-336

**Patient received three doses (50 rad each)

TABLE IV

TOTAL BODY RADIATION

Effect of Previous Therapy on Prodromal Symptomatology
(19 Patients)

Dose		Occurrence of Prodromal Symptoms Pts. with symptoms/Total Pts.	
Midline in air (R)	Midline absorbed (Rad)	No Previous Rx	Previous Rx
<100	<100	0/1	0/1
149-170	100	2/4	2/3
226-255	150	2/3 *	2/2 (1 mild)
294-336	200	2/4 (1 mild)	1/1 (severe)
		6/12 (50%)	5/7 (71%)

* One patient (#013) without symptoms received 3 doses (50 rad each).

TABLE V

Partition of Profile Scores Based on "Net Erythrocyte" Score

Case No.	Disease Score		Radiation Score		Total Score		
	Test	Cumulative	Test	Cumulative	Test	Cumulative	
018	1.4	16.8	12.6	47.2	14.0	64.0	(30)
020	1.73	22.5	4.2	98.2	6.0	120.7	(33)
021	3.8	49.4	12.2	64.2	16.0	113.6	(33)
022	3.8	19.0	4.2	8.0	8.0	27.0	(9)
023	0.4	6.4	1.93	80.6	2.33	87.0	(44)
024	2.66	39.9	12.3	52.7	15.0	92.6	(69)
025	1.7	18.7	17.6	69.3	19.3	88.0	(27)

( ) Days post irradiation.

Data on 026, 027, and 029 inadequate for profile scoring because of technical problems.

TABLE VI

DEOXYCYTIDINE AND THYMIDINE IN RAT URINES BEFORE AND AFTER IRRADIATION (mg/24 hours)

	Deoxycytidine		Thymidine	
	Pooled 1, 2, 3	Pooled 4, 5, 6	Pooled 1, 2, 3	Pooled 4, 5, 6
Control	0	0	.17	.09
1st 24 hrs.	7.3	6.2	1.6	2.5
2nd 24 hrs.	3.0	0	.47	.70
3rd 24 hrs.	1.5	0	.40	.67
4th 24 hrs.	0	0	-	-
5th 24 hrs.	0	0	-	-
7th 24 hrs.	0	0	-	-

- Below minimum amount which could be detected (0.04 mg/24 hrs).

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TABLE VII

DEOXYCYTIDINE AND THYMIDINE IN HUMAN URINES BEFORE AND AFTER IRRADIATION

#027 Patient 1 (Male)	Deoxycytidine mg/hr	Thymidine mg/hr	#029 Patient 2 (Female)	Deoxycytidine mg/hr	Thymidine mg/hr
Control period (24 hour collections)			Control Period (24 hour collections)		
1	-	-	1	-	-
2	-	-	2	-	-
3	-	-	3	-	-
Post-Irradiation Period (6 hour collections)			Post-Irradiation Period (6 hour collections)		
1st 6 hrs.	5.8	5.7	1st 6 hrs.	3.4	-
2nd 6 hrs.	7.8	5.9	2nd 6 hrs.	2.4	-
3rd 6 hrs.	3.8	2.3	3rd 6 hrs.	.90	-
4th 6 hrs.	.75	1.1	4th 6 hrs.	1.8	-
5th 6 hrs.	5.2	1.3	5th 6 hrs.	-	-
6th 6 hrs.	5.0	6.3	6th 6 hrs.	-	-
7th 6 hrs.	1.9	3.4	7th 6 hrs.	-	-
8th 6 hrs.	*	*	8th 6 hrs.	-	-
3rd 24 hrs.	-	-	3rd 24 hrs.	-	-
7th 24 hrs.	-	-	7th 24 hrs.	-	-
10th 24 hrs.	-	-	10th 24 hrs.	-	-
13th 24 hrs.	-	-	13th 24 hrs.	-	-

\- Below minimum amount detectable (0.020 mg/hr)

* Specimen lost

TABLE VIII

URINARY EXCRETION OF XANTHURENIC ACID FOLLOWING WHOLE BODY IRRADIATION µg/ml *

Days	Pt. 023	Pt. 022	Pt. 021	Pt. 027
Pre-treatment				
13-15	0	0	4.4	-
9	0	0	0	-
3	0	0	4.8	0
1	0	15	no spec.	0
Post-treatment				
1	no spec	13	48	6 hrs. 2.3, 12 hrs. 2.6
2	3.2	14	4.4	118 hrs. 0, 30 hrs 2.3, 36hrs 1.6
3	5.2	-	3.2	0
6	-	10	-	0
9	5.0	8	27	-

* Concentrations of XA below 1 µg/ml were not detected.

Pts. 018, 020, 024, 029 showed no detectable XA pre or post irradiation.

APPENDIX A

CLINICAL SUMMARIES

Study No. 018
Patient: H. G.
Chart No. CGH 232557

The patient was a 67 year old white male who had an undifferentiated carcinoma involving trachea and esophagus 20 cm. below the incisors. Biopsy of a right scalene node revealed papillary adenocarcinoma. (Cin. VAS61-1257, 1279, and 1323). He had hemoptysis for 8 weeks. There had been no weight loss, no previous radiation therapy.

On November 5, 1961, he received 200 rad of total body irradiation. Mild nausea occurred for one hour, two hours after completion of therapy. The patient left the hospital on November 6 in order to vote. Eleven days later he complained of increased fatiguability. This symptom progressed with increasing anemia, leucopenia, and thrombocytopenia which were most severe five weeks after total body radiation. The hematological values ultimately returned to pre-treatment levels.

However, the patient's weakness persisted. No improvement in the tumor was noted. With subsequent local irradiation, shrinkage of tumor was accomplished. He expired August 30, 1962, with a tracheoesophageal fistula, 10 months after whole body radiation.

N62-334 Gross Pathological Diagnosis:

1. Carcinoma left main stem bronchus with erosion into the esophagus and fistula formation.
2. Metastases to bone, peripancreatic and para-aortic lymph nodes.
3. Confluent lobular pneumonia with abscess formation, left upper lobe, left lower lobe, right middle lobe and right lower lobe.

Study No. 020
Patient: G. N.
Chart No. CGH 403118

The patient was a 69 year old Negro female who had a combined abdomino-perineal resection for adenocarcinoma of the rectum in March, 1962 (CGH SP 62-491 and SP 62-563). Her postoperative course was uneventful.

On April 22, 1962, she received 200 rad total body radiation. She experienced no untoward symptoms from radiation, but developed leucopenia and thrombocytopenia ten days post therapy. These findings have cleared. As of May, 1963, she has continued to be asymptomatic, one year after irradiation.

Study No. 021
Patient: J. W.
Chart No. CGH 335593

The patient was a 74 year old white male who had the diagnosis of anaplastic carcinoma of the small bowel made in January, 1962 (CGH-SP 62-132). At that time a 5 cm. left upper lobe lung mass was present. There was progression of the lung lesion with subcutaneous extension. There had been some anorexia and nausea prior to therapy.

On April 28, 1962, he was given 200 rad of total body radiation. No change in symptoms of nausea and anorexia followed therapy. Subsequently his course was progressively downhill. Three and one half weeks after therapy anemia, leucopenia and thrombocytopenia became severe. Pneumonia was superimposed and he expired June 3, 1962.

N62-205 Gross Pathological Diagnoses:

1. Anaplastic carcinoma of the left lung with extension to the left pleura, ribs, intercostal muscles, subcutaneous tissue and metastasis to the adrenals, mesentery and jejunum.
2. Caseating tubercular granulomas of the lungs consistent with tuberculosis, active.
3. Pulmonary emphysema and fibrosis, severe.
4. Pulmonary arteriosclerosis, moderately severe.
5. Severe hypoplasia of the bone marrow.

6. Status post-operative jejunectomy and partial resection of the mesentery for removal of a malignant neoplasm and end-to-end anastemosis.

7. Generalized arteriosclerosis, moderate.

8. Coronary arteriosclerosis, moderate.

9. Arteriolar nephrosclerosis, mild.

Study No. 022
Patient: E. J.
Chart No. CGH 369118

The patient was a 48 year old Negro female with carcinoma of the left breast metastatic to lungs, bones, and lymph nodes. A radical mastectomy was performed in January, 1961, and a bilateral oophorectomy in December, 1961. She received 4032 r to the left chest in March, 1961 and 4064 r in air to the lumbar spine in October, 1961. In April, 1962, she received 1700 r per field in air, through two fields to the right hemipelvis.

On May 11, 1962, the patient received 150 rad of total body radiation. She was listless the next day but had no nausea or anorexia. Her course was progressively downhill and she expired May 21, 1962. No autopsy was obtained.

Study No. 023
Patient: B. L.
Chart No. CGH 385615

The patient was a 49 year old Negro male who had the diagnosis of colloid adenocarcinoma of the hepatic flexure of the colon made in September, 1960 (CGH-SP 60-2233). Hepatic enlargement was first noted in August, 1961. At the time of admission his only complaint was of occasional cramping right upper quadrant pain. There was no significant weight loss with weight at 189 pounds.

On May 15, 1962, he was given 200 rad of total body radiation. Anorexia was present for five hours on the day of therapy. Decreased abdominal pain was noted. Four weeks after therapy he had pharyngitis when his white count was 1500. His throat cleared quickly on penicillin. At present he has returned to his pre-therapy state but with less pain in the hepatic area. The patient was ultimately treated with an overall tumor dose of 3000 r to the liver over 24 days, through 20 x 20 cm anterior and posterior quadrant ports. When on this therapy his white count fell to 3900. He was seen in follow-up on March 25, 1963, with a weight of 185 pounds and little abdominal pain. Blood counts had returned to normal. He survives over one year in relatively good health.

Study No. 024
Patient: E. C.
Chart No. CGH 146412

The patient was a 39 year old Negro female who had a metastatic carcinoma from the cervix. She had been treated at Lima Hospital in Lima, Ohio, January, 1961, with external radiation and intracavitary radium, 2200 r through 2 pelvic fields and 4000 r through a transvaginal cone. Radium dose was 4500 mgm. hrs. Left inguinal node biopsy was positive for metastatic squamous cell carcinoma (CGH SP 62-1227). There was metastatic carcinoma (CGH SP 62-1288) on needle biopsy of a neck mass. A nonfunctioning left renal system was noted on intravenous pyelography. Retrograde study revealed narrowing of the lower ureter with hydroureter and caliectasis above. Nodular metastases in the left lung field were seen. Severe pain into the legs caused admission.

On June 10, 1962, the patient received 200 rad of total body radiation. She experienced dizziness, nausea, and vomiting at the conclusion of therapy while in the therapy room. These symptoms cleared within three hours. Post therapeutically, pain was a major problem. Leucopenia and thrombocytopenia occurred six days after therapy, being most severe and associated with anemia at five weeks. Infection (?) with fever occurred at this time but cleared with antibiotic therapy.

Pain has decreased and the patient's sense of well being has returned to pretreatment level. No change in tumor has been noted.

Study No. 025
Patient: J. W.
Chart No. CGH 201454

The patient was a 64 year old Negro male who had colloid carcinoma of the left lung diagnosed in July, 1962. Biopsy of a right preauricular node revealed metastatic colloid carcinoma (CGH SP 62-1990). Symptoms had been cough, left sided pleuritic chest pain, anorexia and weight loss. There had been no previous radiation therapy.

On September 25, 1962, he was given 150 rad of total body radiation. He experienced nausea for one day and vomited four hours after treatment. Subsequently, anorexia, lassitude and weight loss continued.

Four weeks after therapy hemoptysis occurred. This symptom was associated with anemia, leucopenia, and thrombocytopenia. His course continued to be progressively downhill and he expired on October 28, 1962.

Gross Pathological Diagnoses:

1. Carcinoma of bronchus - left lower lobe, mainstem. Extension to left upper lobe, chest wall, and mediastinum. Metastases to liver, spleen, bowel, kidney, adrenal, nodes, thyroid and diaphragm - 2° atelectasis, pneumonia and abscess.
2. Syphilitic aortitis.
3. Moderate arteriosclerotic cardiovascular disease with left ventricular hypertrophy.
4. Arterial nephrosclerosis.
5. Nodular involution of thyroid.

Study No: 026
Patient: F. B.
Chart No: CGH 413142

The patient was a 29 year old white male with the diagnosis of malignant lymphoma (Hodgkins type) made in February, 1963 (CGH SP No. 63-280 and 63-904). He had upper gastroenteric bleeding from an undetermined site. Multiple lymphadenopathy and hepatosplenomegaly were present.

On February 9, 1963, he received 155r midline exposure dose in r equivalent to 100 rad of Co-60 therapy as bilateral total body radiation. No significant change in nausea and vomiting followed this therapy. Little change in the lymphadenopathy or hepatosplenomegaly occurred. Another finding of interest was a non visualizing left kidney on IVP. The patient refused further renal evaluation. The patient insisted on discharge March 8, 1963.

He was readmitted March 21, 1963 with another episode of weakness, but he could not comment on stool color. Intravenous nitrogen mustard (0.2 mgm/kg) was given March 28, 1963 and March 29, 1963. His course has been an unrelenting downhill progression in spite of above plus surgery and local x-ray therapy to his stomach.

Study No.: 027
Patient: D.J.
Chart No.: CGH 400383

The patient was a 17 year old white male with Ewing's Sarcoma (CGH NP 61-144) diagnosed on a biopsy from a sacral spinal tumor in December, 1961. A course of four 450r of Co-60 therapy to the sacrum was given through February 1962. In September, 1962 metastases to the lung with pleural effusion were noted.

On February 23, 1963, a total dose of 238r in r equivalent to 150 rad midline air dose was given as bilateral total body radiation. Severe nausea and vomiting began three hours after exposure. These symptoms persisted for 48 hours. Anorexia lasted for 72 hours. Patient's complaint of chest pain prior to therapy improved, as did the radiological findings, but recurred in four weeks. Four weeks following therapy, anemia, leukopenia, and thrombocytopenia with petechia occurred. Weakness, anorexia, and depression were prominent at this period. Gradual improvement in the hematologic studies occurred so that local mediastinal Co-60 therapy in a dose of 1000r was given in May, 1963. His platelet count and white count were maintained in spite of this therapy, but the anemia persisted.

Study No.: 029
Patient: F.W.
Chart No.: CGH 109436

The patient was a 63 year old white female who had an adenocarcinoma of the left breast with metastases (CGH S.P. No. 61-3080) treated in November, 1961 with a radical mastectomy. All resected nodes were positive. In January of 1962 she completed 3980r tumor dose through the internal mammary port and 3840r to her supraclavicular port. In November, 1962, recurrent carcinoma was present in subcutaneous tissue from the left anterior chest wall. On November 20, 1962 she was placed on Stilbesterol 5 mgm TID which was discontinued in January, 1963.

On March 14, 1963, the patient was given 257r midline air dose in r equivalent to 150 rad of total body radiation. No symptoms referable to the therapy were noted. Anemia to 5.0 gm hemoglobin, leucopenia to the 2500 range and thrombocytopenia were noted at four weeks. She was placed on testosterone propionate 100 mgm three times per week and 200 mgm I.M. three times per week. Studies two months after therapy revealed a normal white and platelet count with a hemoglobin of 12.4 gm.

APPENDIX B

PROFILE SCORING - DESCRIPTION OF METHOD

We have used the profile scoring method of Wald and Thoma (ORNL-2748, Part B). This method provides a way of assigning rank scores for deviations from normality of certain blood values (Appendix B - Table I) and summing them to yield test scores which can be related to clinical degrees of injury.

In performing these calculations we calculated a disease mean daily test score based on the "net erythrocyte" scores (Appendix B - Table II). The DMTS is assumed to represent the daily contribution of the underlying disease to the total test score following radiation. Thus a mean disease score was subtracted from the total daily post-treatment score.

To illustrate the calculations a sample profile score sheet is appended with the derivation of each column (Appendix B - Table II). Appendix B - Table III indicates the calculations on a representative patient.

APPENDIX B - TABLE 1

PROFILE VALUES ASSIGNED FOR VARIOUS RANGES OF ABNORMALITY

HEMATOLOGY--PERIPHERAL COUNTS

TEST	UNITS	NORMAL*	PROFILE VALUE							
			1	2	3	4	1	2	3	4
			(for increase above normal)				(for decrease below normal)			
Hemoglobin	gm. per cent	M-15.8	18	19	20	21	14	12	10	8
		F-13.9	16	17	18	19	11.5	10	8.5	7
Erythrocytes	Mill./mm.^{3}	M- 5.4	6.0	7.0	8.0	9.0	4.5	3.5	2.5	1.5
		F- 4.8	5.5	6.5	7.5	8.5	4.0	3.0	2.0	1.0
Hematocrit	Volume per cent	M-47	54	56	58	60	40	35	30	25
		F-42	47	49	51	53	37	32	27	22
Leukocytes	1,000/mm.^{3}	7.4	12	18	24	30	4.0	3.0	2.0	1.0
Neutrophils	1,000/mm.^{3}	4.4	7.7	14	21	28.0	1.8	1.3	0.9	0.5
Lymphocytes	1,000/mm.^{3}	2.5	4.8	7.0	10	12.0	1.0	0.75	0.5	0.3
Platelets	1,000/mm.^{3}									
Rees-Ecker		405	545	700	850	1000	273	200	100	30
Brecher-Cronkite		257	440	600	750	900	140	100	50	30
Fonio		234	350	500	650	800	130	100	50	30
Dameshek		716	900	1000	1500	2000	500	350	100	30
Reticulocytes	per cent red blood cells	1.5	4	8	15	25	0.5	0		
Erythrocyte Sedimentation Rate	mm./hr.	M-5	10	20	30	40				
		F-10	20	30	40	50				

* Expressed as "universal mean" value. Taken from Standard Values in Blood: Being the First Fascicle of a Handbook of Biological Data. E.C. Albritton, Editor. W.B. Saunders Company, Philadelphia, 1952.

APPENDIX B - TABLE II

SAMPLE PROFILE SCORE SHEET

1	2	3		4		5		6		7		8		9		10		11		12		13	
STT	Day of Observ.	Hgb.		RBC		Hct.		Net RBC		WBC		Neutrophile		Lymph		Platelet		Disease Score		Radiation Score		Total Score	
		T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C

T = test score

C = cumulative score

Col 1 — STT refers to standard test times (Thoma & Wald)

Col 2 — Day of observation corresponding to standard test time

Col 3,4,5 — Profile score based on observed Hgb, Rbc, and Hct.

Col 6 — Calculated "net erythrocyte" score, i.e., $T_6 = \frac{T_3 + T_4 + T_5}{3}$ $\qquad C_6 = \frac{C_3 + C_4 + C_5}{3}$

Col 7,8,9,10 — Profile score based on observed Wbc, Neutrophile, Lymphocyte and Platelet Counts

Col 11 — T_{11} = Calculated disease mean daily test score (DMTS) = $\frac{C_{11} \text{ (at end of pre Rx period)}}{\text{No. of observations prior to Rx}}$

In the post Rx period T_{11} = DMTS
In the post Rx period C_{11} = DMTS x number of observations in the post Rx period

Col 12 — T_{12} (Radiation test score) = $T_{13} - T_{11}$
C_{12} (Radiation cumulative score) = $C_{13} - C_{11}$

Col 13 — T_{13} (Total test score) = $T_6 + T_7 + T_8 + T_9 + T_{10}$
C_{13} (Total cumulative score) = $C_6 + C_7 + C_8 + C_9 + C_{10}$

#007 JT, age 62, cm

APPENDIX B - TABLE III

PROFILE SCORE SHEET - TOTAL BODY RADIATION STUDY

1	2	3		4		5		6		7		8		9		10		11		12		13	
STT	Day of Observ.	Hgb.		RBC		Hct.		Net RBC		WBC		Neutrophile		Lymph		Platelet		Disease Score		Radiation Score		Total Score	
		T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Pre-Rx																							
	21	1	1	0	0	1	1	.66	.66	0	0	0	0	0	0	0	0	.66	.66				
	18	1	2	0	0	0	1	.33	.99	0	0	0	0	2	2	1	1	3.33	3.99				
	16	1	3	0	0	0	1	.33	1.32	0	0	0	0	0	2	0	1	.33	4.32				
	14	1	4	0	0	0	1	.33	1.65	0	0	0	0	0	2	0	1	.33	4.65				
	10	1	5	0	0	0	1	.33	1.98	0	0	0	0	0	2	0	1	.33	4.98				
	8	0	5	0	0	0	1	.00	1.98	0	0	0	0	0	2	1	2	1.00	5.98				
	2	1	6	0	0	0	1	.33	2.31	0	0	0	0	0	2	0	2	.33	6.31				
Calculated Disease Mean Daily Test Score (DMTS																		.9					
Post-Rx																							
1	1	1	1	0	0	0	1	.33	.33	0	0	0	0	2	2	2	2					4.33	4.33
2	2	1	2	0	0	0	1	.33	.66	0	0	0	0	2	4	0	2					2.33	6.66
3	3	1	3	0	0	0	1	.33	.99	0	0	0	0	2	6	0	2					2.33	8.99
6	6	1	4	0	0	1	2	.66	1.65	0	0	0	0	4	10	0	2					4.66	13.65
9	9	1	5	1	1	1	3	1.00	2.65	2	2	1	1	4	14	1	3					9.00	22.65
12	12	2	7	1	2	1	4	1.33	3.98	2	4	1	2	4	18	1	4					7.33	29.98
15	14	2	9	0	2	1	5	1.00	4.98	1	5	0	2	4	22	1	5					7.00	36.98
18	17	2	11	0	2	1	6	1.00	5.98	1	6	0	2	4	26	2	7					8.00	44.98
21	20	1	12	1	3	1	7	1.00	6.98	3	9	1	3	4	30	2	9					11.66	56.64
24	24	2	14	2	5	1	8	1.66	8.64	3	12	2	5	4	34	3	12					13.66	70.30
27	28	2	16	2	7	1	9	1.66	10.30	3	15	2	7	4	38	3	15		9.9	12.76	74.10	13.66	83.96

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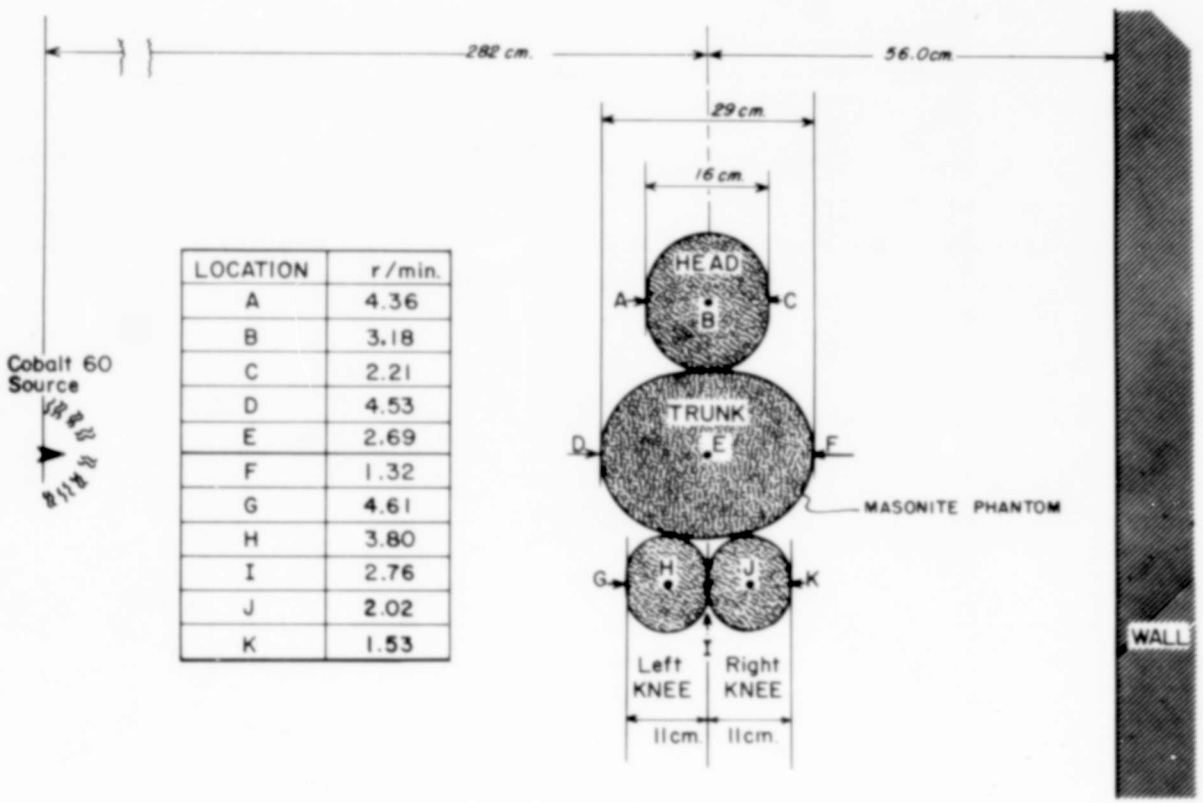
FIGURE I

Dosimeter Measurements in a Masonite Phantom



LOCATION	r/min.
A	4.36
B	3.18
C	2.21
D	4.53
E	2.69
F	1.32
G	4.61
H	3.80
I	2.76
J	2.02
K	1.53

FIGURE II

Relative Depth Dose for Lateral Exposures

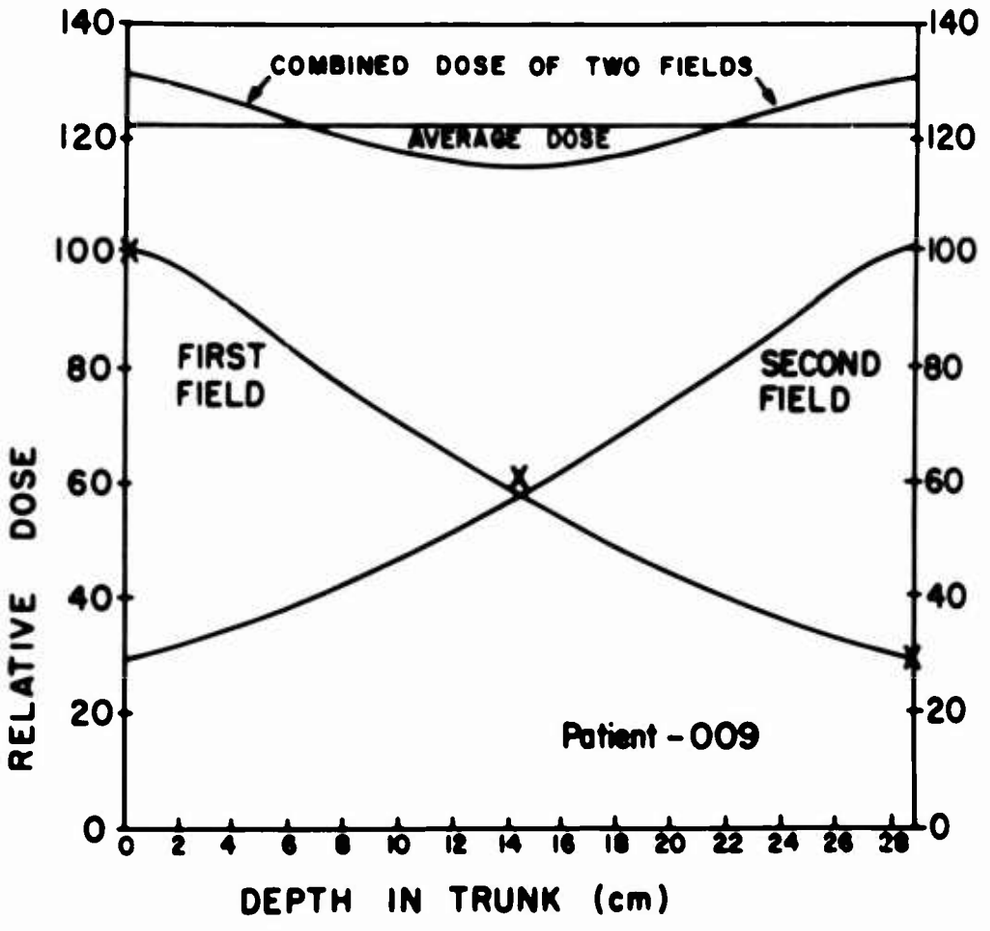


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FIGURE III

Endoreduplication of Chromosomes 6 hours Post Radiation (#029)

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Results and conclusions from this research include:

a. A new technique has been developed for identification of deoxycytidine, presumably a breakdown product of DNA. Deoxycytidine has been identified in urine following whole body irradiation.

b. Xanthurenic acid, an end product of tryptophane metabolism, has been found in the urine of some of the patients after whole body irradiation.

c. Chromosomal abnormalities have been identified in white cells immediately after irradiation.

d. Human beings can tolerate doses of 200 rad (300 r) relatively well as far as combat effectivness is concerned, but it is probable that a second dose of the order of 200 rad, even after apparent complete recovery, will result in a significant number of individuals becoming combat ineffective immediately.

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